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Adherence to the Mediterranean diet and risk of bladder cancer in the EPIC cohort study.

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Running head: The Mediterranean diet and bladder cancer in EPIC

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Abbreviations: rMED, relative Mediterranean diet; BMI, Body Mass Index; EPIC, European Prospective Investigation; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases for Oncology; MD, Mediterranean diet; SD, Standard deviation.

What's New?: Urothelial cell carcinoma (UCC) is the most common form of bladder cancer. Previous studies suggested that plasma carotenoids, antioxidants found in fruit and vegetables, were associated with a decreased risk of UCC while a high intake of animal protein was associated with an increased cancer risk. Here, the authors conducted the first study to investigate the association between the Mediterranean diet, a diet rich in fresh fruits and vegetables and low in animal products, and UCC in Europe. They found that adherence to a Mediterranean diet was not significantly associated with UCC, regardless of level of tumour aggressiveness. They point out that these findings are in line with the rather weak evidence for questionnaire-based associations between dietary factors and bladder cancer risk.

Abstract

There is evidence on the protective role of the Mediterranean diet on cancer. However, to date no epidemiological study to date has investigated the influence of the Mediterranean diet on bladder cancer. Therefore, we evaluated the association between adherence to the Mediterranean diet and risk of urothelial cell bladder cancer (UCC), according to prognostic risk group (tumor aggressiveness), in the European Prospective Investigation into Cancer and Nutrition (EPIC).

The analysis included 477,312 participants, recruited from ten European countries between 1991 and 2000. Information from validated dietary questionnaires was used to develop a relative Mediterranean diet score (rMED), including nine dietary components. Cox regression models were used to assess the effect of the rMED on UCC risk, while adjusting for dietary energy and tobacco smoking of any kind. Stratified analyses were performed by sex, BMI, smoking status, European region and age at diagnosis. During an average follow-up of 11 years, 1,425 participants (70.9% male) were diagnosed with a first primary UCC. There was a negative but non-significant association between a high versus low rMED score and risk of UCC overall (HR: 0.84 [95% CI 0.69, 1.03]) and risk of aggressive (HR: 0.88 [95% CI 0.61, 1.28]) and non-aggressive tumors (HR: 0.78 [95% CI 0.54, 1.14]). Although there was no effect modification in the stratified analyses, there was a significant 34% ($p = 0.0043$) decreased risk of UCC in current smokers with a high rMED score. In EPIC, the MD was not significantly associated with risk of UCC, although we cannot exclude that a MD may reduce risk in current smokers.

Introduction

There is evidence that the Mediterranean dietary pattern has a protective role on risk of overall and specific types of cancer incidence and mortality.(1-4) To our knowledge though, no epidemiological study to date has investigated the influence of the Mediterranean diet (MD) on bladder cancer. Bladder cancer is the eighth most common type of cancer in the world (5) and established risk factors include tobacco smoking, occupational exposure to aromatic amine carcinogens and *Schistosoma haematobium* infection (6-7).

Various dietary factors have also been suggested to be related to bladder cancer.^{8,9} However, the 2007 WCRF/AICR report⁶ concluded that the strength of evidence was “limited” to conclude that specific food groups, such as fruit and vegetables, fat, meat or red meat and dairy products, modify bladder cancer risk. Since the WCRF/AICR report, the European Prospective Investigation into Nutrition and Cancer (EPIC) study, the same cohort analyzed in this article, has published results showing that plasma carotenoids (important antioxidants found primarily in fruit and vegetables) were associated with a decreased risk of urothelial cell carcinoma (UCC), the predominant cell type of bladder cancer. In addition, both a high intake of energy from animal protein and a low intake of energy from plant protein were related to increased risk of UCC in this cohort (10).

Therefore, there is tentative evidence that certain features characteristic of the MD pattern (a plant-based diet rich in antioxidants such as carotenoids and relatively low in animal-derived products and animal protein), may have a beneficial effect on the risk of bladder cancer. Consequently, we aimed to investigate the association

between adherence to the Mediterranean dietary pattern and risk of UCC within the EPIC cohort.

MATERIAL AND METHODS

Study population and data collection

EPIC is an ongoing prospective cohort study involving 23 centres in 10 European countries (Denmark, France, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom). The full rationale, methods and design details have been described previously (11,12). In brief, 521,454 participants aged mostly 25-70 years old were recruited from 1992-2000, mainly from the general population or defined geographical area, town or province, but with some exceptions (12). At baseline validated country-specific questionnaires were used to record the usual diet during the previous year and to capture local dietary patterns (12,13). Lifestyle questionnaires were used to obtain information on socio-demographic characteristics, physical activity, medical history, and alcohol and tobacco consumption. Anthropometric measures were also ascertained at recruitment.

All participants gave written informed consent and the relevant ethics committees approved the study. Participants were excluded if they had been registered as having cancer previously or if they had missing end of follow-up data (n = 28,289), missing information on diet or lifestyle (n = 6,253) or a ratio for energy intake versus energy expenditure in the top and bottom 1% (n = 9,600), leaving 477,312 participants for the current analysis.

Outcome Assessment

Incident bladder cancer cases were identified by population cancer registries for Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom. A combination of methods were used in France, Germany and Greece, as detailed previously.(12). Mortality data were also obtained from regional or national mortality registries. Censoring dates for the last complete follow-up ranged from December 2004 to June 2010, depending on the center. The follow-up period was defined from age at recruitment until age at diagnosis of a first cancer (of any type), death or last complete follow-up, depending on which occurred first. Participants diagnosed with a cancer other than bladder cancer during follow-up were censored at the date of diagnosis of their first tumor. Cases were defined as subjects with a first primary bladder cancer, coded as C67 using International Classification of Diseases for Oncology Third Edition (ICD-O-3), which occurred during follow-up. The analysis only included the urothelial cell papillomas and transitional cell carcinomas (morphology/behavior codes 8120/1, 8120/2, 8120/3, 8122/3, 8130/1, 8130/2 and 8130/3), as these make up more than 90% of bladder tumors, and they are referred to now on as urothelial cell carcinomas (UCC).¹⁰ Other bladder cancer morphologies were censored at date of diagnosis (10,14). The UCC cases were separated into relatively aggressive (high risk of progression) and non-aggressive (low risk of progression), (15) as described previously.(16) Tumor aggressiveness was only classified for bladder cancer cases diagnosed up until 2007, as these have been individually validated by pathology reports, and the remaining tumors were censored at date of diagnosis for stratified analyses.

The relative Mediterranean diet (rMED) score

Level of adherence to a traditional MD was estimated using the relative Mediterranean diet score (rMED),(17) an adapted version of the original MD score by Trichopoulou et al. (18). The rMED is an 18-point linear score that incorporates nine key dietary components; seven components presumed to reflect the MD (fruit, nuts and seeds [one component combined], vegetables, legumes, fish, olive oil and cereals) and two components presumed not to reflect the MD (dairy products and meat), calculated as a function of energy density (g/day/2,000 kcal) and divided into tertiles. The scoring system has been detailed previously.(17) The rMED also includes alcohol, scored by assigning two to moderate consumers (ranging from 5 to 25 g/day for women and 10–50 g/ day for men) and 0 to participants outside this sex-specific range. The rMED score ranged from 0 to 18 (lowest to highest adherence).

Statistical Analysis

Analyses were preformed using Stata version 10 (Statacorp, College Station, TX). Cox proportional hazards regression models were used to assess the association between the rMED score and UCC risk. Age was the primary time variable used. All models were stratified by sex, age at EPIC study entry (1 year intervals) and EPIC center. All models were adjusted for total energy intake (kcal/day, continuous), smoking status (11 categories: never smoker (never smoked tobacco of any kind but exposed or unknown exposure to second-hand smoke at work/home), true never smokers (never smoked tobacco of any kind and never exposed to second-hand smoke at work/home), current smokers who smoke 1–15, 16–25, ≥ 26 cigarettes/day at recruitment, former smokers who quit <10, 10–19, ≥ 20 years ago, current occasional smoker of cigarettes or other types of tobacco, current/former smokers with unknown intensity or time since cessation and unknown smoking status and cigarette

smoking duration for current and former smokers (six categories: never, <10, 10–19, 20–29, ≥30 years and unknown). The following variables that were tested in the model, BMI, education level, milk and animal protein intake, did not affect the model parameters and consequently were not included in the final models. All models met the proportional hazard assumption, tested using the Schoenfeld goodness-of-fit test.

The rMED score was assessed as a continuous variable (per 4-unit) and as a categorical variable (low, medium and high). Additional models were created to assess the risk of UCC by tumor aggressiveness and age at diagnosis, using the Wald statistic to assess the homogeneity of risk between outcomes. Plausible effect modification was explored for sex, smoking status (never, former, current [all] and current heavy long-term smokers defined as smokers of ≥15 cigarettes/ day at baseline who have smoked for ≥15 years), BMI (<25 vs. ≥25 kg/m²) and European Region (Northern, Middle and Southern). Interaction terms were modeled between each of these separate variables and the categorical rMED score, and tested using the log-likelihood ratio test, while adjusting for energy intake and smoking status and duration. Sensitivity analyses included repeating the analysis (i) excluding the first 2 years of follow-up to control for potential changes in diet due to early symptoms of bladder cancer, (ii) using an rMED score excluding alcohol, since alcohol is a recognized risk factor for many cancers⁶ and (iii) using an rMED score replacing olive oil intake with the commonly used lipid ratio (monounsaturated plus polyunsaturated fatty acids divided by saturated fatty acids).

RESULTS

Participants (477,312) were followed-up for a mean of 11.0 years (>4.5 million person-years). During this period 1,575 first primary bladder cancer cases were diagnosed (Table 1), of which 1,425 (70.9% male) were UCC. In The Netherlands, the proportion of male cases was slightly lower, most likely due to fewer males overall. According to tumor stage and grade, 430 were aggressive and 413 were non-aggressive UCC tumors and for 582 subjects tumor aggressiveness was unknown (n=52) or not validated (n=530). The mean rMED score was 8.6 (SD 3.2), and was highest in Greece, Italy and Spain and lowest in Sweden and The Netherlands. Table 2 shows the baseline characteristics of the cohort according to level of adherence to the MD. In general, participants with a higher rMED score were more likely to be women, younger, never smokers and to have a higher education level, lower energy intake and to consume less milk and animal protein. The adjusted HRs for risk of UCC by categories of the rMED score are presented in Table 3. There was a negative but non-significant association between a high versus low rMED score and risk of UCC overall (HR: 0.84 [95% CI 0.69, 1.03]) and risk of aggressive (HR: 0.88 [95% CI 0.61, 1.28]) and risk of non-aggressive tumors (HR: 0.78 [95% CI 0.54, 1.14]). When the rMED score was analyzed per 4-unit increase, the HR for risk of UCC was 0.95 (95% CI 0.87, 1.03) (data not shown). There was no evidence that the relation between the MD and UCC was modified by sex, age at diagnosis, BMI or European region (Table 3). However, when the association was assessed by smoking status, there was a significant inverse association between a high versus low score rMED score and UCC in current smokers (HR: 0.66 [95% CI 0.47, 0.93]), which was more pronounced in current heavy and long-term smokers (HR: 0.51 [95% CI 0.31, 0.86]) (data not shown). However, the interaction between smoking status (current, former, never) and the rMED score did not reach statistical significance. In

sensitivity analyses, the HR for a high versus low rMED score did not materially change after excluding the first 2 years of follow-up (HR: 0.89 [95% CI 0.72, 1.10]), when using a rMED excluding alcohol (HR 0.82 [95% CI 0.67, 1.02]) or when using an rMED including a fat ratio instead of olive oil (HR 0.88 [95% CI 0.73, 1.06]).

DISCUSSION

There is evidence that the Mediterranean dietary pattern has a protective role on risk of overall and specific types of cancer incidence and mortality (1–4). To our knowledge though, no epidemiological study to date has investigated the influence of the Mediterranean diet (MD) on bladder cancer. Bladder cancer is the eighth most common type of cancer in the world (5) and established risk factors include tobacco smoking, occupational exposure to aromatic amine carcinogens and *Schistosoma haematobium* infection (6,7). Indeed, previous studies in EPIC (19,20) and other cohorts (21,22) have found no overall effect of consumption of fruit and vegetables (19,21,22) as measured from dietary questionnaires, on bladder cancer risk. However, research in EPIC on dietary biomarkers has shown more promising results; higher plasma levels of carotenoids were associated with a decreased risk of UCC and there was a prominent protective effect of carotenoids and also vitamin C in current smokers.¹⁶ In line with this, we observed that a high rMED score was related to a significantly decreased risk of UCC in current smokers, especially among heavy long-term smokers. Although this finding should be interpreted with caution, since the interaction was not significant, it is biologically plausible that smokers may benefit more from following a MD, and this interaction is supported by previous epidemiological studies in other tumors (23). One theory is that the MD's high antioxidant content (i.e., vitamin C, E, carotenoids, flavonoids and polyphenols) could

reduce or prevent the DNA damaging effect of free radicals and oxidants in cigarette smoke(23). The MD's favorable fatty acid profile, with a high content of essential omega-3 fatty acids, could also be relevant for the inflammatory effects from tobacco smoke exposure(23). However, we cannot rule out that potential residual confounding by smoking could partly explain these results, since no association was observed in never smokers. The traditional MD also includes a relatively low consumption of red and processed meat and animal protein, which could also be beneficial for reducing risk of bladder cancer, as previous cohort studies have reported an increased risk of bladder cancer associated with dietary nitrites from processed meat²⁴ and a high energy intake from animal protein(10). Therefore, certain dietary features of the MD and their potentially anti-carcinogenic mechanisms make an association plausible from a mechanistic point of view. Despite this, we found no evidence, at least not statistically significant, that the MD affected the overall risk of bladder cancer. However, the limitations of our study should be considered when interpreting the results, including potential measurement errors derived from dietary questionnaires, which could lead to systematic and random errors when estimating adherence to the MD. Although our adjustment for total energy intake would partly remove some of these errors(25) we cannot rule out that they have attenuated risk estimates and therefore could partly explain the lack of significant association we observed. In addition, we were unable to take into account any possible changes in dietary and lifestyle habits over time, although this would most likely have only attenuated the risk estimates as well. Finally, there were fewer female compared to male cases, which could have reduced the statistical power and accounted for the wider confidence intervals in female stratified analyses. The strengths of this study include its prospective design, long follow-up and multi-centric

European design covering a wide range of dietary intakes and lifestyle habits. In addition, we focused on UCC tumors only, to limit possible differential effects of the MD on other (rare) bladder cancer histologies. We also had sufficient information to be able to analyse UCC tumors according to risk of progression, which may influence its etiology, and evaluate whether certain cohort characteristics modified the relationship between the MD and bladder cancer. Since tobacco smoking is the most important bladder cancer risk factor we carefully adjusted for its potentially confounding effect by including smoking intensity, duration, time since quitting and exposure to second-hand smoke in all statistical models, and by presenting results stratified by smoking status. However, some residual confounding by tobacco smoking could still remain. The rMED score uses tertiles of intake as cut-offs instead of the frequently used medians, to give a better distribution of the subjects with different intakes. In summary, this is the first prospective study to examine the association between the MD and bladder cancer, and we found no conclusive evidence that this dietary pattern was related to bladder cancer risk. However, we cannot rule out that the MD may decrease the risk of UCC in current smokers, especially in heavy long-term smokers. Some studies have also observed only suggestive associations between the MD and overall cancer or certain cancers such as endometrial cancer.³ Nevertheless, in general the epidemiological evidence supports the protective role of the MD in overall cancer mortality and incidence, and in specific cancers of the stomach, colorectum and breast^(3,4,17). Thus, the MD remains a good choice for cancer prevention in Europe.

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Table 1. Distribution of participants and bladder cancer cases and mean Mediterranean diet score across the 10 EPIC countries

Country	Total Cohort (% male)	Person- years	Bladder Cancer Cases				rMED, ² mean (SD)
			Total (% male)	Urothelial cell carcinomas (% male)	Aggressive Urothelial cell carcinomas ¹ (% male)	Non-aggressive Urothelial cell carcinomas ¹ (% male)	
France	67,385 (0)	699,360	31 (0)	24 (0)	13 (0.0)	6 (0)	9.8 (2.6)
Italy	44,541 (31.5)	500,407	183 (69.4)	143 (67.1)	45 (60.0)	42 (66.7)	11.0 (2.3)
Spain	40,002 (37.9)	482,582	146 (82.8)	138 (82.6)	24 (70.3)	61 (90.2)	11.2 (2.4)
UK	75,395 (30.3)	838,397	251 (69.7)	234 (72.7)	57 (66.7)	67 (73.1)	9.3 (2.7)
The Netherlands	36,505 (26.4)	431,252	104 (48.1)	101 (49.5)	30 (50.0)	29 (44.8)	6.3 (2.3)
Greece	26,032 (41.5)	247,711	45 (84.4)	25 (84.0)	5 (80.0)	6 (83.3)	12.8 (1.9)
Germany	48,583 (43.6)	480,614	199 (70.9)	171 (71.9)	46 (71.7)	40 (90)	7.3 (2.4)
Sweden	48,684 (43.6)	638,931	289 (74.7)	281 (74.7)	90 (72.2)	80 (78.8)	5.0 (2.3)
Denmark	55016 (47.8)	601,466	303 (79.2)	284 (79.6)	112 (74.1)	80 (90.0)	7.0 (2.7)
Norway	35,169 (0)	342,279	24 (0)	24 (0)	8 (0.0)	2 (0)	8.0 (2.2)
TOTAL	477,312 (29.8)	4563639	1,575 (70.4)	1,425 (70.9)	430 (65.6)	413 (77.7)	8.6 (3.2)

Abbreviations: EPIC: European prospective investigation into cancer and nutrition. rMED: relative Mediterranean diet score. ¹Includes only cases diagnosed before 2007 with tumor aggressiveness validated by pathology reports (582 cases with unknown or not validated tumour aggressiveness).

²rMED score: ranges from 0 (lowest adherence) to 18 (highest adherence) and includes 9 components; vegetables, legumes, fruit and nuts, cereals, fresh fish and seafood, olive oil, alcohol, meat and dairy products.

Table 2. Baseline characteristics of the 477,312 participants in the EPIC cohort according to level of adherence to the Mediterranean diet score

Characteristics	Whole cohort (n=477,312)	rMED score ¹		
		Low (131,522)	Medium (206,353)	High (139,437)
Male, %	29.8	40.5	25.4	26.7
Age at enrolment, mean years	51.2 ± 9.9	51.8 ± 10.1	51.5 ± 9.5	50.4 ± 10.3
BMI, mean kg/m ²	25.4 ± 4.3	25.6 ± 4.2	25.2 ± 1.2	25.7 ± 4.5
Height, mean cm	166.0 ± 8.9	168.9 ± 9.1	165.8 ± 8.6	163.5 ± 8.5
Weight, mean kg	70.2 ± 13.7	73.2 (14.2)	69.4 ± 13.4	68.6 ± 13.0
Energy intake, mean kcal/d	2,074.0 ± 619.2	2,124.3 ± 650.5	2,044.5 ± 606.2	2,070.3 ± 604.2
Smoking status, %				
Never ²	41.3	38.0	41.0	44.9
Never and no secondhand exposure ³	1.7	1.4	1.9	1.8
Current, 1-15 cigarettes/d	11.6	14.3	11.2	9.7
Current, 16-25 cigarettes/d	6.3	8.7	5.5	5.1
Current >26 cigarettes/d	1.8	2.0	1.4	2.3
Former smoker, quitting <10y ago	9.6	9.3	9.4	10.0
Former smoker, quitting 10-19y ago	8.2	7.8	8.5	8.1
Former smoker, quitting ≥20y ago	7.9	8.1	8.9	6.2
Current occasional cigarette smoker/ other types of tobacco	8.4	7	8.8	9.1
Current/Former, unknown intensity/ quitting time	1.6	2.1	1.8	1.0
Unknown	1.7	1.3	1.8	1.9
Smoking duration, %				
Never	43.0	39.4	42.9	46.7
<10 years	6.9	6.4	7.4	6.6
10-19 years	10.5	9.6	10.6	11.1
20-29 years	13.5	13.6	13.4	13.4
≥30 years	16.0	23.2	14.7	11.2
Missing	10.2	7.9	11.0	11.1
Educational level, %				
No formal education	4.4	0.6	3.0	10.1
Primary school	25.6	30.2	22.4	26.0
Secondary school	20.4	17.8	21.5	21.4
Technical or Professional training	22.3	30.2	23.4	13.1
University degree	23.8	19.0	25.4	25.9
Not specified	3.6	2.2	4.4	3.5
Milk intake, mean g/d	199.0±211.9	286.6±259.5	190.2±195.8	129.6±145.9
Animal protein intake, mean g/1000kcal/d	25.3±8.8	26.5±8.1	25.9±8.9	23.3±8.9

All comparison between groups and tests for trend statistically significant at $p < 0.001$. EPIC: European prospective investigation into cancer and nutrition. ¹rMED: relative Mediterranean Diet Score includes 9 components: vegetables, legumes, fruit, cereals, fresh fish, olive oil, alcohol, meat and dairy products from EPIC dietary questionnaire data (Low Score: 0 to 6, Medium Score: 7 to 10, High Score: 11 to 18). ²Never smokers (of cigarettes or other types of tobacco) but exposed to second-hand smoke (at home or work) or not known if exposed to second-hand smoke. ³Never smokers (cigarettes nor other types of tobacco) and never exposed to second-hand smoke (at home or work).

Table 3. Association between adherence to the Mediterranean diet and UCC bladder cancer in EPIC, by participants characteristics

Stratified by ¹	No. cases/ population	rMED score - categorical			P-trend	P-heterogeneity
		Low HR (95% CI) ¹	Medium HR (95% CI) ²	High HR (95% CI) ²		
Overall						
No. cases/ population	1,425/477,312	588/ 131,522	565/ 206,353	272/ 139,437		
Total Cohort	1,425/477,312	1 [Referent]	0.94 (0.83, 1.07)	0.84 (0.69, 1.03)	0.107	N/A
Tumour Aggressiveness						
Non-aggressive	413/ 477,312	1 [Referent]	0.87 (0.69, 1.90)	0.78 (0.54, 1.14)	0.147	
Aggressive	430/ 477,312	1 [Referent]	0.89 (0.69, 1.13)	0.88 (0.61, 1.28)	0.405	0.657 ⁴
Age at diagnosis						
<65 years	656/ 477,312	1 [Referent]	0.84 (0.69, 1.02)	0.81 (0.61, 1.07)	0.102	
≥65 years	769/ 477,312	1 [Referent]	1.02 (0.86, 1.21)	0.86 (0.64, 1.14)	0.504	0.756 ⁴
Sex						
Men	1010/ 141,240	1 [Referent]	0.95 (0.81, 1.01)	0.79 (0.62, 1.01)	0.094	
Women	415/ 335,062	1 [Referent]	0.92 (0.73, 1.18)	0.95 (0.68, 1.33)	0.692	0.709 ⁵
Smoking Status ²						
Current smokers (all)	586/107,089	1 [Referent]	0.92 (0.76, 1.14)	0.66 (0.47, 0.93)	0.043	
Current heavy smokers ³	291/45760	1 [Referent]	0.77 (0.57, 1.05)	0.51 (0.31, 0.86)	0.011	
Former Smokers	518/ 127,148	1 [Referent]	0.85 (0.69, 1.05)	0.97 (0.71, 1.33)	0.529	
Never Smokers	309/ 233,342	1 [Referent]	1.15 (0.86, 1.55)	1.08 (0.71, 1.64)	0.617	0.581 ⁵
BMI						
<25kg/m ²	507/ 246,837	1 [Referent]	0.98 (0.79, 1.21)	0.92 (0.66, 1.28)	0.637	
≥25kg/m ²	918/ 230,475	1 [Referent]	0.93 (0.79, 1.10)	0.82 (0.64, 1.06)	0.138	0.321 ⁵
European Region						
Northern	589/ 138,869	1 [Referent]	0.94 (0.79, 1.14)	0.93 (0.60, 1.44)	0.535	
Middle	523/ 199,849	1 [Referent]	0.93 (0.76, 1.12)	0.85 (0.62, 1.17)	0.288	
Southern	313/ 138,594	1 [Referent]	0.89 (0.45, 1.76)	0.78 (0.39, 1.54)	0.237	0.832 ⁵

Abbreviations: UCC; Urothelial cell carcinoma, EPIC; European Prospective Investigation into Cancer and Nutrition.
rMED: relative Mediterranean diet score.

¹Cox models stratified by sex, age at diagnosis and center and adjusted for energy intake, smoking status (including exposure to secondhand smoke in never smokers), smoking intensity, duration and time since quitting (where

²Smoking status strata exclude 9,733 individuals (12 cases) with missing information on smoking status

³Current heavy smokers includes current smokers of ≥15 cigarettes/day and for ≥15years duration

⁴Wald test for homogeneity

⁵Log likelihood ratio test.